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Relation of Beta-Blocker–Induced Heart Rate Lowering and Cardioprotection in Hypertension

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Objectives The purpose of this study was to evaluate the role of heart rate reduction with beta-blockers on the risk of cardiovascular events in patients with hypertension.

Background Resting heart rate has been shown to be a risk factor for cardiovascular morbidity and mortality in the general population and in patients with heart disease such as hypertension, myocardial infarction, and heart failure. Conversely, pharmacological reduction of heart rate is beneficial for patients with heart disease. However, the role of pharmacological reduction of heart rate using beta-blockers in preventing cardiovascular events in patients with hypertension is not known.

Methods We conducted a MEDLINE/EMBASE/CENTRAL database search of studies from 1966 to May 2008. We included randomized controlled trials that evaluated beta-blockers as first-line therapy for hypertension with follow-up for at least 1 year and with data on heart rate. We extracted the baseline characteristics, the blood pressure response, heart rate at the baseline and end of trial, and cardiovascular outcomes from each trial.

Results Of 22 randomized controlled trials evaluating beta-blockers for hypertension, 9 studies reported heart rate data. The 9 studies evaluated 34,096 patients taking beta-blockers against 30,139 patients taking other antihypertensive agents and 3,987 patients receiving placebo. Paradoxically, a lower heart rate (as attained in the beta-blocker group at study end) was associated with a greater risk for the end points of all-cause mortality ($r = -0.51$; $p < 0.0001$), cardiovascular mortality ($r = -0.61$; $p < 0.0001$), myocardial infarction ($r = -0.85$; $p < 0.0001$), stroke ($r = -0.20$; $p = 0.06$), or heart failure ($r = -0.64$; $p < 0.0001$). The same was true when the heart rate difference between the 2 treatment modalities at the end of the study was compared with the relative risk reduction for cardiovascular events.

Conclusions In contrast to patients with myocardial infarction and heart failure, beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients. (J Am Coll Cardiol 2008; 52:1482–9) © 2008 by the American College of Cardiology Foundation

Resting heart rate has been shown to be an independent risk factor for cardiovascular morbidity and mortality for patients without cardiovascular disease (1), for patients with acute myocardial infarction (MI) (2) or hypertension (3,4), and for patients with known coronary artery disease (CAD) (5,6).

Given that higher resting heart rate is a risk factor, slowing it should have beneficial effects. In fact, exercise is a well-known intervention serving to lower resting heart rate and to increase survival. Kjekshus et al. (7), in a meta-analysis of randomized controlled trials (RCTs) of acute MI and post-MI trials, showed that reduction of heart rate by beta-blockers is closely related to reduction in infarct size (in acute MI trials) and to reduction in mortality and nonfatal MI in long-term trials. Similar beneficial effects of heart rate reduction have been observed in meta-analyses of RCTs of patients with heart failure (8) and angina pectoris. As a result of these studies, it has become a common clinical contention to ascribe the "cardioprotective" effect of beta-blockers to their heart lowering effect: the slower the heart rate, the greater the benefit.

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Whether the beneficial effects of heart rate reduction with a beta-blocker are applicable to patients with hypertension is not known.

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Methods

Search strategy. Eligible trials had to fulfill the following criteria to be included in this analysis: 1) RCTs with comparison of regimen based on beta-blockers with other agents (including placebo) in patients with hypertension; 2) beta-blocker usage as first-line therapy for hypertension; 3) follow-up of at least 1 year; and 4) evaluation of cardiovascular outcomes data on heart rate.

Data sources and study search. We conducted a MEDLINE/EMBASE/CENTRAL search of studies using the terms "beta adrenergic blockers," "adrenergic beta antagonist," "beta-blockers," and "hypertension." We limited our search to studies in human subjects and in the English language in peer-reviewed journals from 1966 to May 2008. We checked the reference lists of reviewed articles, prior meta-analyses, and original studies identified by the electronic search to find other potentially eligible studies. Trials that were only in abstract form without a manuscript published were not considered for this analysis.

Study selection. Two authors (S.B. and S.S.) independently assessed trial eligibility ($\kappa = 0.96$). Disagreements were resolved by consensus.

End points and data extraction. Outcomes of interest were all-cause mortality, cardiovascular mortality, MI, stroke, and heart failure considered separately. We extracted the inclusion/exclusion criteria, publication year, sample size, age, first-line antihypertensive agents used, blood pressure and heart rate before randomization and at the end of the study, length of follow-up, and the above outcomes of interest for each of the studies.

Statistical analysis. Statistical analysis was done using standard software (Stata 9.0, Stata Corp., College Station, Texas) using the METAN program (9). The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). Heterogeneity was assessed using Q (chi-square) statistics and/or the I^2 statistics (10). If trials were homogeneous ($p > 0.10$), a fixed-effect model was used to calculate pooled effect sizes. Otherwise, a random-effects model of DerSimonian and Laird (11) was applied to calculate overall differences. Publication bias was estimated using the weighted regression test of Egger.

Meta-regression analysis. Meta-regression analyses were performed to evaluate the relationship between heart rate at treatment end on beta-blocker therapy and the risk of cardiovascular outcomes. A curve fit analysis was performed to evaluate the best regression fit. The analysis was weighted by the weight of each trial for the specific outcomes. The p value was considered significant at <0.05.

Results

We identified 22 RCTs in which beta-blockers were used as first-line agents, patients were followed up for at least 1 year, and cardiovascular outcomes were evaluated. Of the 22 RCTs, 9 trials had data on heart rate and were included for this analysis (Fig. 1). We excluded the results from the MAPHY (Metoprolol Atherosclerosis in Hypertension) trial (12), as this was a subgroup from the HAPPHY (Heart Attack Primary Prevention in Hypertension trial) (13).

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
MI = myocardial infarction
RCT = randomized controlled trial
RR = relative risk

Characteristics of the trials. The baseline characteristics and inclusion criteria are summarized in Tables 1 (14–21) and 2. The 9 RCTs evaluated 68,220 patients with hypertension: 34,096 patients (50%) randomly assigned to the beta-blocker arm, 3,987 (6%) randomly assigned to placebo, and 30,137 (44%) randomly allocated to other antihypertensive agents. Of the patients in the beta-blocker arm, 26,527 (78%) received atenolol, 3,185 (9%) received oxprenolol, 275 (1%) received propranolol, and 4,109 (12%) received atenolol/metoprolol/pindolol or hydrochlorothiazide. In the comparison group, 3,987 patients (12%) were given placebo, 4,605 patients (13%) received angiotensin-receptor blockers, 3,603 (11%) received diuretics, and 21,929 (64%) received calcium-channel blockers.

Beta-blocker versus comparison baseline characteristics. The average (weighted) mean age of the patients in the trials was 58 years, and patients were followed up for a mean of 3.5 years (Table 3). The beta-blocker and the comparison groups were similar with respect to the mean age, follow-up duration, and baseline systolic and diastolic pressures (weighted). In the beta-blocker group, the average weighted baseline systolic pressure decreased by 13.5% (166.2 ± 14.6

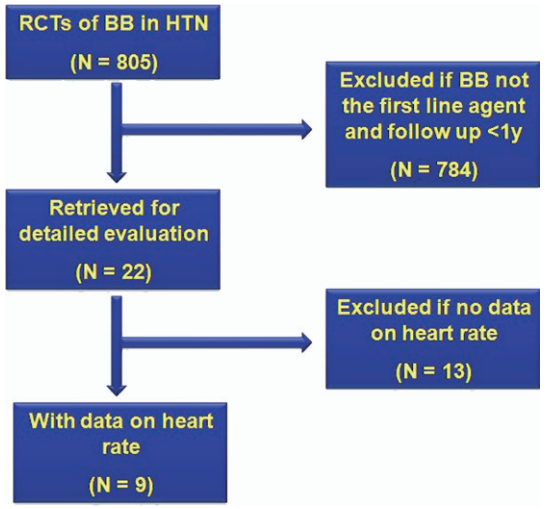

Figure 1 Selection of Studies

BB = beta-blockers; HTN = hypertension; RCT = randomized controlled trial.

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Table 1 General Characteristics of Included Trials

Trial (Ref. #), Year	Patient Characteristics	Number of Patients	Follow-Up (yrs)	Beta-Blocker	Comparison
Versus placebo					
IPPPSH (14), 1985	Hypertension but no CAD	6,357	4.0	Oxprenolol	Placebo
STOP (15), 1991	Hypertension but no MI, angina, or stroke in prior 12 months	1,627	2.1	Atenolol/metoprolol/pindolol/ HCTZ/amiloride	Placebo
Versus other antihypertensive agents					
ASCOT (16), 2005	Hypertension and at least 1 other cardiovascular risk factor but no CAD	19,257	5.5	Atenolol	Amlodipine
ELSA (17), 2002	Hypertension; excluded patients with no baseline or <1 follow-up carotid ultrasound	2,334	3.8	Atenolol	Lacidipine
HAPPHY (13), 1987	Hypertension without MI, angina, CVA	6,569	3.8	Atenolol or metoprolol	Bendrofluazide/HCTZ
INVEST (18), 2003	CAD and hypertension	22,576	2.7	Atenolol	Verapamil SR
LIFE (19), 2002	Hypertension and LVH; no MI or CVA in prior 6 months	9,222	4.8	Atenolol	Losartan
VACS (20), 1982	Men with hypertension (DBP 95–114 mm Hg)	394	1	Propranolol	HCTZ
Yurenev et al. (21), 1992	Men with hypertension (>160/95 mm Hg) and different degree of LVH and no CAD	304	4	Propranolol	Diuretic

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; BFZ = bendrofluazide; CAD = coronary artery disease; CVA = cerebrovascular accident; DBP = diastolic blood pressure; ELSA = European Lacidipine Study on Atherosclerosis; HAPPHY = Heart Attack Primary Prevention in Hypertension trial; HCTZ = hydrochlorothiazide; INVEST = International Verapamil SR and Trandolapril study; IPPPSH = International Prospective Primary Prevention Study in Hypertension; LIFE = Losartan Intervention for End point Reduction trial; LVH = left ventricular hypertrophy; MI = myocardial infarction; STOP = Swedish Trial in Old Patients With Hypertension; VACS = Veterans Administration Cooperative Study Group on Antihypertensive Agents.

mm Hg to 143.8 ± 10.6 mm Hg; $p < 0.0001$) and the diastolic blood pressure by 14.2% (100.4 ± 6.8 mm Hg to 86.1 ± 6.7 mm Hg; $p < 0.0001$) (Table 3). Similarly, in the comparison group, the average weighted baseline systolic pressure decreased by 13.1% (166.7 ± 14.7 mm Hg to 144.9 ± 17.3 mm Hg; $p < 0.0001$) and the diastolic blood pressure by 13.3% (100.4 ± 7.3 mm Hg to 87 ± 7.7 mm Hg; $p < 0.0001$) (Table 3). There was no difference between the final attained systolic and diastolic blood pressure between the beta-blocker and the comparison groups. However, beta-blockers caused a significant decrease (12%) in heart rate, whereas the comparison group had a nonsignificant decrease (1%) in heart rate. Thus, there was a 12% lower heart rate in the beta-blocker group compared with the comparison agent at the end of the trial ($p < 0.0001$) (Table 3).

Cardiovascular mortality. For the outcome of cardiovascular mortality (7 RCTs reporting this outcome), the risk reduction was comparable between the beta-blocker group and the comparison group (3.3% vs. 3.0%; pooled relative risk [RR]: 1.05; 95% confidence interval [CI]: 0.88 to 1.25; $p = 0.615$). Given heterogeneity in the analysis (heterogeneity chi-square = 18.11 [df = 7]; $p = 0.011$; $I^2 = 61.4\%$; $Tau^2 = 0.0283$), a random effects model was used. However, the tests for publication bias were negative (Begg's test $p = 0.902$; Egger's $p = 0.650$).

Table 2 General Characteristics of Included Trials: Hemodynamics

Trial (Ref. #)	Mean Age (yrs)	Men (%)	BB HR (beats/min) Baseline/Final	Controls HR (beats/min) Baseline/Final	Mean Baseline BP (mm Hg)	Study End BP (BB–Controls) (mm Hg)
Versus placebo						
IPPPSH (14)	52	100	79.8/72	80.1/77	173/108	−3.8/−1.2
STOP (15)	76	37	77/NR	76/NR	195/102	−19.5/−8.1
Versus other antihypertensive agents						
ASCOT (16)	63	77	71.8/61.3	71.9/72.5	164/95	+2.7/+1.9
ELSA (17)	56	55	76/66	76.3/76.3	163/101	+1.5/−0.2
HAPPHY (13)	52	100	77/64	77/75	166/107	−0.0/−1.0
INVEST (18)	66	48	75.5/69.2	75.6/72.8	151/87	<1
LIFE (19)	67	46	73.7/66	73.9/72.1	174/98	+1.1/−0.2
VACS (20)	50	100	77/60.9	76.6/79.5	145/101	+9.2/+1.8
Yurenev et al. (21)	45	100	70.2/66	68.8/68.6	168/106	+3.4/+1.4

BB = beta-blocker; BP = blood pressure; HR = heart rate; NR = not reported; other abbreviations as in Table 1.

Table 3 Summary Statistics of the Included Trials

Variable	Beta-Blocker (n = 34,096)	Comparison (n = 34,124)	p Value
Age, yrs	58 ± 10	58 ± 10	1.000
Follow-up, yrs	3.5 ± 1.4	3.5 ± 1.4	1.000
Systolic BP baseline, mm Hg	166.2 ± 14.6	166.7 ± 14.7	0.948
Diastolic BP baseline, mm Hg	100.4 ± 6.8	100.4 ± 7.3	0.986
Systolic BP final, mm Hg	143.8 ± 10.6	144.9 ± 17.3	0.874
Diastolic BP final, mm Hg	86.1 ± 6.7	87 ± 7.7	0.790
Heart rate baseline, beats/min	75 ± 3	75 ± 3	0.584
Heart rate final, beats/min	66 ± 4	74 ± 3	<0.0001

BP = blood pressure.

The relationship between heart rate at the end of treatment and risk of cardiovascular mortality followed an inverse linear relationship ($y = 3.5913 - 0.0375x$; $r = -0.6133$; $p = 0.00001$), so that the relative risk of cardiovascular mortality increased with decreasing heart rate at treatment end (Fig. 2).

Nonfatal MI. For the outcome of nonfatal MI (8 RCTs reporting this outcome), the risk reduction was comparable between the beta-blocker group and the comparison group (3.2% vs. 3.0%; pooled RR: 1.05; 95% CI: 0.96 to 1.14; $p = 0.275$). There was no heterogeneity in the analysis (heterogeneity chi-square = 5.34 [df = 8]; $p = 0.721$; $I^2 = 0.0\%$; $Tau^2 = 0.0000$). The tests for publication bias were negative (Begg's test $p = 0.917$; Egger's $p = 0.490$).

The relationship between heart rate at the end of treatment and risk of nonfatal MI followed an inverse linear relationship ($y = 0.8788 - 0.021x$; $r = -0.6948$; $p = 0.00001$) so that the relative risk of nonfatal MI increased with decreasing heart rate at treatment end (Fig. 3). A similar inverse linear relationship was also seen when the difference in heart rate at treatment end was plotted against the risk of nonfatal MI, suggesting that the more efficacious beta-blockers were at reducing heart rate, the greater the risk of nonfatal MI (Fig. 4).

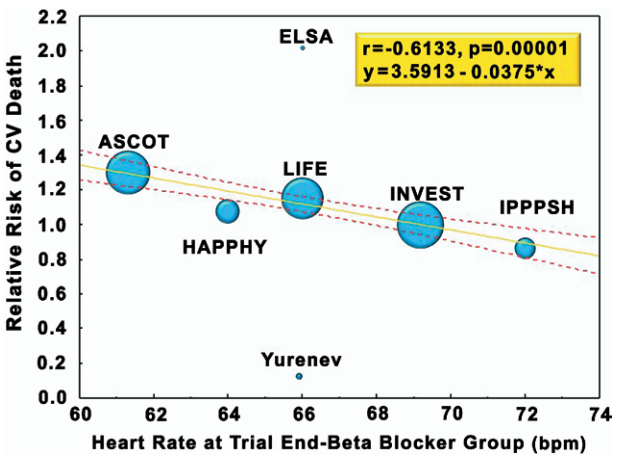

Figure 2 Risk of Cardiovascular Mortality as Function of Heart Rate

Relative risk of cardiovascular mortality as a function of heart rate achieved at the end of the study in the beta-blocker group. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; bpm = beats/min; CV = cardiovascular; ELSA = European Lacidipine Study on Atherosclerosis; HAPPHY = Heart Attack Primary Prevention in Hypertension; INVEST = International Verapamil SR and Trandolapril study; IPPSH = International Prospective Primary Prevention Study in Hypertension; LIFE = Losartan Intervention for End point Reduction trial.

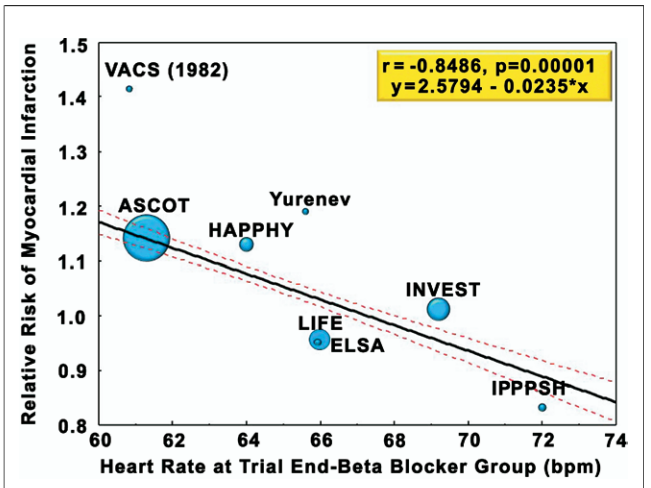

Figure 3 Risk of Nonfatal MI as Function of Heart Rate

Relative risk of nonfatal myocardial infarction (MI) as a function of heart rate achieved at the end of the study in the beta-blocker group. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. VACS = Veterans Administration Cooperative Study Group on Antihypertensive Agents; other abbreviations as in Figure 2.

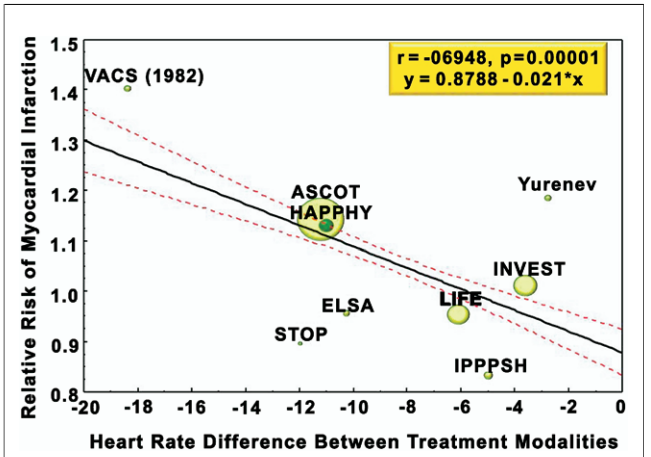

Figure 4 Risk of Nonfatal MI as Function of Heart Rate Difference Between Treatments

Relative risk of nonfatal MI as a function of heart rate difference between treatment modalities. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. STOP = Swedish Trial in Old Patients With Hypertension; other abbreviations as in Figure 2.

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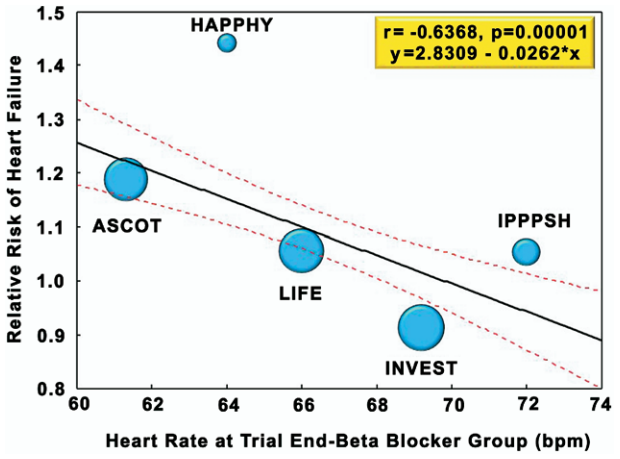

Figure 5 Risk of HF as Function of Heart Rate

Relative risk of heart failure (HF) as a function of heart rate achieved at the end of the study in the beta-blocker group. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. Abbreviations as in Figure 2.

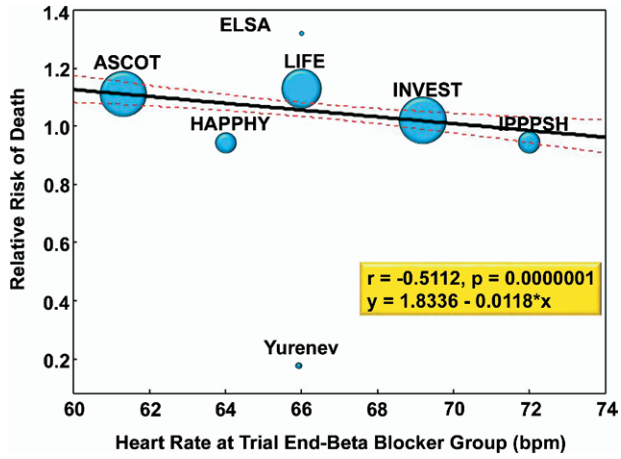

Figure 7 Risk of All-Cause Mortality as Function of Heart Rate

Relative risk of all-cause mortality as a function of heart rate achieved at the end of the study in the beta-blocker group. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. Abbreviations as in Figure 2.

Heart failure. For the outcome of heart failure (5 RCTs reporting this outcome), the risk reduction was comparable between the beta-blocker group and the comparison group (1.8% vs. 1.8%; pooled RR: 1.00; 95% CI: 0.83 to 1.22; p = 0.959). Given heterogeneity in the analysis (heterogeneity chi-square = 11.73 [df = 5]; p = 0.039; I^2 = 57.4%; Tau^2 = 0.0295), a random effects model was used. The tests for publication bias were negative (Begg's test p = 0.851; Egger's p = 0.927).

The relationship between heart rate at the end of treatment and risk of heart failure followed an inverse linear relationship (y = 2.8309 − 0.0262x; r = −0.6368, p = 0.00001) so that the relative risk of heart failure increased with decreasing heart rate at treatment end (Fig. 5).

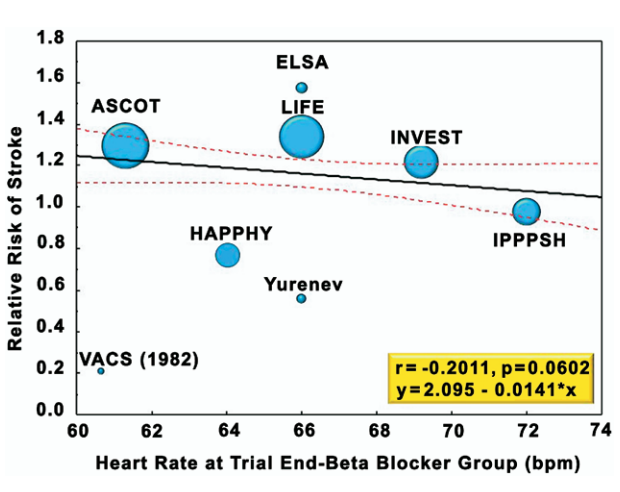

Figure 6 Risk of Stroke as Function of Heart Rate

Relative risk of stroke as a function of heart rate achieved at the end of the study in the beta-blocker group. The **diameter of the circles** represents the weight of each individual trial. The **line** represents the regression fit with 95% confidence interval for the effect sizes. Abbreviations as in Figure 2.

Stroke. For the outcome of stroke (8 RCTs reporting this outcome), the risk reduction was comparable between the beta-blocker group and the comparison group (2.8% vs. 2.3%; pooled RR: 1.04; 95% CI: 0.84 to 1.28; p = 0.746). Given heterogeneity in the analysis (heterogeneity chi-square = 23.39 [df = 8]; p = 0.003; I^2 = 65.8%; Tau^2 = 0.0497), a random effects model was used. The tests for publication bias were negative (Begg's test p = 0.251; Egger's p = 0.063).

The relationship between heart rate at the end of treatment and risk of stroke showed a trend toward an inverse linear relationship (y = 2.095 − 0.0141x; r = −0.2011; p = 0.0602) so that the relative risk of stroke trended to increase with decreasing heart rate at treatment end (Fig. 6).

All-cause mortality. For the outcome of all-cause mortality (7 RCTs reporting this outcome), the risk reduction was comparable between the beta-blocker group and the comparison group (7.0% vs. 6.7%; pooled RR: 1.01; 95% CI: 0.90 to 1.13; p = 0.870). Given heterogeneity in the analysis (heterogeneity chi-square = 17.01 [df = 7]; p = 0.017; I^2 = 58.9%; Tau^2 = 0.0112), a random effects model was used. However, the tests for publication bias were negative (Begg's test p = 0.711; Egger's p = 0.238).

The relationship between heart rate at the end of treatment and risk of all-cause mortality followed an inverse linear relationship (y = 1.8336 − 0.0118x; r = −0.5112; p = 0.0000001) so that the relative risk of all-cause mortality increased with decreasing heart rate at treatment end (Fig. 7).

Discussion

This systematic review of RCTs investigated the role of heart rate on the risk of cardiovascular events in patients with hypertension treated with a beta-blocker. In contrast to patients with MI, heart failure, and known CAD, a slower heart rate with a beta-blocker was associated with increased risk of cardiovascular events and death among hypertensive patients: the slower the heart rate, the greater the risk.

Resting heart rate in health. In persons with no known cardiovascular disease, a faster heart rate is associated with an increased risk of cardiovascular events. In the Framingham cohort of 5,070 subjects free of cardiovascular disease at entry who were followed up for 30 years, for both genders, at all ages, all-cause, cardiovascular, and coronary mortality rates increased progressively in relation to antecedent heart rates determined biennially (1). Similarly, in a study of 8,916 men in 3 Chicago epidemiological studies, mortality from both cardiovascular and noncardiovascular causes generally increased with increasing heart rate (22). Other studies in the U.S. and United Kingdom have found an association between heart rate and cardiovascular events among patients without cardiovascular disease (23,24). The hypothesis put forward to explain this association is that a higher resting heart rate may be an indicator of increased sympathetic activity, which has been implicated in the development of cardiovascular disease risk factors (25) such as hypertension (26) and diabetes mellitus (27) and has been directly related to coronary heart disease morbidity (28) and mortality (29), including sudden cardiac death (30) and total mortality (31).

Conversely, physical activity and endurance training decreases resting heart rate and has been documented to reduce cardiovascular morbidity and mortality. The favorable effect of aerobic conditioning has been attributed to a reduction in the sympathetic activity and an increase in the parasympathetic activity that, in addition to other myriad effects, also results in a decrease in heart rate. However, there are no data showing that pharmacological reduction of heart rate in persons free of cardiovascular disease has any beneficial effects.

Resting heart rate in cardiovascular disease. Among the 24,913 patients with suspected or proven CAD from the CASS (Coronary Artery Surgery Study) registry followed up for 14.7 years, all-cause and cardiovascular mortality as well as cardiovascular rehospitalization rates were increased with increasing heart rate ($p < 0.0001$) (5). Similarly, in the acute MI cohort (SPRINT-2 [Secondary Prevention Reinfarction Israeli Nifedipine Trial-2] and GISSI-2 [Gruppo Italiano per lo Studio della Saprawivenza nell'Infarto Miocardico-2] studies), in-hospital mortality increased with increased admission heart rate (32,33). Similar results have been shown within the post-MI cohort as well. In patients with known CAD (previous MI, revascularization, or angina), a higher heart rate results in higher work load on the heart in the presence of a compromised coronary circulation.

Although higher heart rate was a poor prognostic indicator in this cohort, pharmacological reduction of heart rate has proven to reduce this risk. Kjekshus et al. (7) in a meta-analysis of acute MI trials showed that a reduction in heart rate of at least 15 beats/min during infarct evolution was associated with a reduction of infarct size between 25% and 30%. In an analysis of post-MI trials, a relationship between actual reduction in heart rate by using a beta-blocker and reduction in mortality ($r = 0.60$) and nonfatal reinfarctions ($r = 0.59$) was seen (7). Kjekshus et al. (7) hypothesized that the beneficial effect of beta-blockers was related to a quantitative reduction in heart rate, probably indicating an anti-ischemic effect. Similarly, among patients with stable angina as well as among post-MI patients (34), heart rate lowering calcium-channel blockers were found to exert beneficial effects (35). In the INITIATIVE (International Trial of the Antianginal Effects of Ivabradine Compared to Atenolol) trial (36), ivabradine, a new I(f) inhibitor that acts specifically on the pacemaker activity of the sinoatrial node and hence may be considered as a pure heart rate lowering agent, was found to be noninferior to atenolol for patients with stable angina, emphasizing the role of heart rate in patients with angina. Similarly, in patients with heart failure, drugs that increase heart rate (positive inotropic substances) augment mortality, whereas drugs that decrease heart rate (beta-blockers) reduce mortality (8).

Resting heart rate in hypertension. Among 4,530 untreated hypertensive patients (blood pressure >140 mm Hg systolic or >90 mm Hg diastolic) patients in the Framingham study, the risk of cardiovascular events increased with increased resting heart rate, with an odds ratio for each 40 beats/min increment in heart rate of 1.68 to 1.70 (95% CI: 1.08 to 2.67) for cardiovascular mortality and 2.14 to 2.18 (95% CI: 1.59 to 2.88) for all-cause mortality (1). Similar results have been shown in other studies in the hypertensive cohort (37).

However, no study to date has shown that pharmacological reduction of heart rate is beneficial for patients with hypertension. To the contrary, the results of the present analyses show that reduction of heart rate with beta-blocker therapy is associated with increased risk of cardiovascular events.

To some extent, our findings could be explained by an increase in central aortic pressure and/or pulse pressure with pharmacological heart rate lowering. The central aortic pressure depends on wave reflection from the periphery. In patients with slower heart rate, the reflected wave reaches the next wave in systole (instead of diastole), and hence may increase central aortic pressure. Thus, pharmacologically induced bradycardia leads to dyssynchrony or uncoupling between outgoing and reflected wave, thereby elevating central aortic pressure. In fact, in the CAFE (Conduit Artery Functional End Point) study (38), for the same peripheral blood pressure, 4.3 mm Hg higher central aortic systolic blood pressure and 3.0 mm Hg higher central aortic pulse pressure were noted with atenolol-based treatment

compared with the amlodipine-based treatment, resulting in a 14% higher risk of coronary events and 23% increase in stroke rate. The CAFE study suggested that the central aortic systolic blood pressure (measured indirectly by radial artery applanation tonometry) may be more predictive of cardiovascular events than the traditional peripheral (brachial) blood pressure measurements. A second possible explanation of our findings could be related to an increase in pulse pressure. As mean arterial pressure is a product of cardiac output (heart rate × stroke volume) and peripheral vascular resistance, a decrease in heart rate with a beta-blocker should result in higher stroke volume, serving to maintain cardiac output. A higher stroke volume, in turn, results in increased systolic pressure and decreased diastolic pressure, thus elevating the pulse pressure. Pulse pressure has been identified as an independent predictor of cardiovascular events among patients with hypertension (39).

Study limitations. As in other meta-analyses, given the lack of data in the each trial, we did not adjust our analyses for dose of medications used or for compliance with assigned therapy. Although we have shown an association between risk of cardiovascular events and heart rate, further studies are needed to establish causation. It should also be noted that the beta-blocker used in the studies was mainly atenolol, and hence, any meaningful extrapolation of these results to other beta-blockers, including the newer vasodilating beta-blockers, should be done with caution. We have used relative risk (beta-blockers vs. controls) in each of the studies as a function of heart rate achieved. Given that all of the trials were RCTs, the baseline characteristics between the beta-blocker and the comparison group were well matched. However, given lack of patient level data, we were unable to control for between-study differences in the baseline clinical characteristics.

Conclusions

In contrast to patients with MI and heart failure, beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients. Pharmacologically-induced bradycardia may lead to dyssynchrony between outgoing and reflected pulse wave, thereby increasing central aortic pressure and the hemodynamic burden to the target organs.

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